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(54) PREVENTIVE OR THERAPEUTIC AGENT FOR NEUROPATHIC PAIN

(57) The present invention provides medicinal agents that are useful for the prevention or treatment of neuropathic pain which comprises as an active ingredient a β2 adrenoceptor stimulant. In addition, the present invention provides formulations for the prevention or treatment of neuropathic pain such as painful diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, or postoperative or traumatic chronic pain, that are **characterized by** the use in combination of an α_2-adrenoceptor stimulant and a β_2-adrenoceptor stimulant, or by containing a compound that has both α_2-adrenoceptor stimulation and β_2-adrenoceptor stimulation activities as an active ingredient or the like.

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Description

Field of the invention

[0001] The present invention relates to formulations that are useful for the prevention or treatment of neuropathic pain.

[0002] More specifically, the present invention relates to a formulation for the prevention or treatment of neuropathic pain that comprises as an active ingredient a β_2-adrenoceptor (hereinafter referred to as β_2 AR) stimulant, a combination formulation for the prevention or treatment of neuropathic pain that are characterized by comprising an α_2-adrenoceptor (hereinafter referred to as α_2 AR) stimulant and a β_2-AR stimulant and the like.

Background Art

[0003] Neuropathic pain is defined as pain caused or induced when the nervous system is injured temporarily or is in dysfunction. The pain is an intractable algetic disease, as it is resistant to antiphlogistic analgesics and anesthetic analgesics. The typical diseases include cancerous pain, postherpetic neuralgia, trigeminal neuralgia, phantom limb pain, causalgia and painful diabetic neuropathy (or diabetic painful neuropathy) and the like. Among neuropathic pain diseases, particularly prevalent is painful diabetic neuropathy. It is conjectured that the number of such patients will increase further as that of diabetic patients increases along with changes in life style and aging of the population. Patients with the above-mentioned diseases have pain and sensory abnormality characterized by hyperalgesia and allodynia. It has been reported that because said symptoms persist, patients often suffer from insomnia, loss of appetite or reactive depression, markedly affecting adversely the QOL of patients (for example, see Non-patent reference 1).

[0004] The etiology of neuropathic pain remains mostly unknown. It is conjectured that the disease is induced partially by peripheral and central neuropathy at various levels, and pain is manifested as a metabolic abnormality, either at peripherally or centrally, blood flow disorder and degeneration of nerve fiber, and changes in synaptic responsiveness lie complexly one upon another.

[0005] Neuropathic pain is treated with pharmacotherapy and nerve block therapy. Drugs used in pharmacotherapy include anticonvulsants, psychotropic vitamins, non-steroidal anti-inflammatory drugs, aldose reductase inhibitors, hypoglycemic drugs and lidocaine-like antiarrhythmic drugs. Nerve block therapy includes stellate nerve block, continuous epidural block, nerve root block and the like. However, because hypersusceptibility to neuropathic pain is caused by the breakdown of balance between conduction system and suppression system of pain, these treatments are often insufficiently effective. Quick development of new drugs is hoped.

[0006] It is known that α_2 AR stimulants lower blood pressure and peripheral vascular resistance and are useful for the treatment of hypertension, cancerous pain by epidural administration (that is, epidural block), postoperative pain and so on (for example, see Non-patent reference 2). It was reported that α_2 AR stimulants demonstrated analgesic action in rats with peripheral nerve disorders (Non-patent reference 3). However, α_2 AR stimulants are not used practically as the systemic therapeutic agent for neuropathic pain partly because of problems of central adverse effects, particularly, sedation, sleepiness, dizziness, thirstiness and so on.

[0007] It is known that β_2 AR stimulants suppress smooth muscle contraction and so on and are useful as bronchodilator, the therapeutic agent of imminent abortion and premature labor, pain relief and lithagogue for uretero-lithiasis and so on (for example, see Patent reference 1 and Non-patent reference 4). It was also reported that a β_2 AR stimulant improved nerve blood flow in rat diabetic neuropathy models (Non-patent reference 5). However, there is no report that β_2 AR stimulants are effective analgesics for neuropathic pain. Furthermore, as it has been suggested that β_2 AR stimulants at high doses may increase blood sugar levels in diabetic patients; no studies have been conducted on β_2 AR stimulants as painkiller for diabetic neuropathy.

[0008] As mentioned above, it is not known at all that β_2 AR stimulants alleviate neuropathic pain, or a combination of an α_2 AR stimulant and a β_2 AR stimulant is more effective for neuropathic pain than the sole use of either agent.

[0009]

[Patent reference 1] International publication No. 97 - 30023 pamphlet
[Non-patent reference 1] Katsuyuki Moriwaki et al.: Pain Clinic, Vol. 21, May 2000, Supplement pp.S101-S107
[Non-patent reference 2] Shuji Dohi.: The Japanese Journal of Clinical Medicine, 2001, Vol. 59, pp.1800-1805
[Non-patent reference 3] Frederic Duflo et al.: Anesthesiology, 2002, Vol. 97, pp.636-641
[Non-patent reference 4] Chikako Tanaka et al. (ed) New Pharmacology, pp.227-236, 2002 (Nankodo)
[Non-patent reference 5] Mary A. Cotter et al.: European Journal of Pharmacology, 1998, Vol. 343, pp.217-223

Disclosure of the invention

Problem that the invention aims to solve

[0010] The purpose of the present invention is to provide therapeutic formulations for neuropathic pain.

Means to solve the problem

[0011] As the result of strenuous research on the above-mentioned problem, the inventors found, to our surprise, that, by administering a β_2 AR stimulant, the combination of an α_2 AR stimulant and a β_2 AR stimulant or a compound that has both α_2 AR stimulation and β_2 AR stimulation activities, neuropathic pain was alleviated in diabetic rats induced by streptozotocin (hereinafter referred to as STZ) and Seltzer model rats, and thereby forming the basis of the present invention.

[0012] That is, the present invention relates to:

[1] a formulation for the prevention or treatment of neuropathic pain, which comprises a β_2-adrenoceptor stimulant as an active ingredient;
[2] a formulation for the prevention or treatment of neuropathic pain as described in the above [1], which comprises the combination of an α_2-adrenoceptor stimulant and a β_2-adrenoceptor stimulant;
[3] a formulation as described in the above [2], which comprises as an active ingredient a compound that has both α_2-adrenoceptor stimulation and β_2-adrenoceptor stimulation activities;
[4] a formulation as described in the above in any of the above [1] to [3], wherein neuropathic pain is painful diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, phantom limb pain, causalgia, cancerous pain, or postoperative or traumatic chronic pain;
[5] a formulation as described in any of the above [1] to [4], which can be used in combination with one or more of drugs selected from a group consisting of a psychotropic vitamins, a non-steroidal anti-inflammatory drug, an aldose reductase inhibitor, a lidocaine-like anti-arrhythmic drug, an antidepressant and an anticonvulsant;
[6] a method of the prevention or treatment of neuropathic pain, which comprises repeated administration of effective doses of a β_2-adrenoceptor stimulant for 2 weeks or longer;
[7] a method of the prevention or treatment of neuropathic pain, which comprises administration of effective doses of the combination of an α_2-adrenoceptor stimulant and a β_2-adrenoceptor stimulant;
[8] a use of a β_2-adrenoceptor stimulant for the manufacture of a formulation for the prevention or treatment of neuropathic pain;
[9] a use of an α_2-adrenoceptor stimulant and a β_2-adrenoceptor stimulant for the manufacture of a formulation the prevention or treatment of neuropathic pain; and the like.

Effect of the invention

[0013] Combination formulations of the present invention which contain an α_2 AR stimulant and a β_2 AR stimulant demonstrated extremely effective analgesic action in STZ-induced diabetic rats and Seltzer model rats, and are therefore useful for the prevention or treatment of neuropathic pain.

Brief description of the drawing

[0014] [Figure 1] Analgesic effects of sole and combination administrations (in repeated administration) of an α_2 AR stimulant and a β_2 AR stimulant in STZ-induced diabetic rats are shown. The axis of abscissas in the figure denotes administration groups, wherein Normal indicates a normal group, Control indicates a control group, Clon L indicates a clonidine L group (0.1 mg/kg), Clon M indicates a clonidine M group (0.3 mg/kg), TB L indicates a terbutaline L group (1 mg/kg), TB M indicates a terbutaline M group (3 mg/kg), Combi1 indicates a combination L-L group (combination of clonidine 0.1 mg/kg and terbutaline 1 mg/kg), Combi2 indicates a combination L-M group (combination of clonidine 0.1 mg/kg and terbutaline 3 mg/kg), Combi3 indicates a combination M-L group (combination of clonidine 0.3 mg/kg and terbutaline 1 mg/kg), and Combi4 indicates a combination M-M group (combination of clonidine 0.3 mg/kg and terbutaline 3 mg/kg). The symbol "**" means $P<0.01$ (significant difference from Control in Steel test), and "##" indicates $P<0.01$ (significant difference from Control in Aspin-Welch's t test).

[0015] [Figure 2] Analgesic effects of a compound which has both α_2 AR stimulation and β_2 AR stimulation activities (in repeated administration) in STZ-induced diabetic rats are shown. The axis of abscissas in the figure denotes administration groups, wherein Normal and Control have the same meanings as described in the above Figure 1. Numerals denote doses of compound 1 (mg/kg). The symbols "**" and "##" denote the same meanings as described in the above

Figure 1.

[0016] [Figure 3] Analgesic effects of a compound which has both a_2 AR stimulation and β_2 AR stimulation activities (in single administration) in Seltzer model are shown. The axis of abscissas in the figure denotes administration groups wherein Normal is the normal group. The symbol "**" indicates P<0.01 (significant difference from the pre-administration value (two corresponding groups were tested). The symbol "#" indicates P<0.05 (significant difference in pre-administration values between normal group and nerve ligation group in Aspin-Welch's t test).

[0017] [Figure 4] Analgesic effects of a compound which has both α_2 AR stimulation and β_2 AR stimulation (in repeated administration) in Seltzer model are shown. The axis of abscissas in the figure denotes administration groups, wherein Normal and Control have the same meanings as described in the above Figure 1. The symbol "**" indicates P<0.01 (significant difference from the control group in Aspin-Welch's t test).

Best mode to operate the invention

[0018] As α_2 AR stimulants; any known α_2 AR stimulant may be used. Such agents include, for example, clonidine, moxonidine, rilmenidine, medetomidine, dexmedetomidine, guanfacine, guanabenz, α-methylnoradrenaline, methyldopa, UK14304, B-HT920 and B-HT933.

[0019] A dosage of an α_2 AR stimulant may be determined as needed according to individual α_2 AR stimulant, patients' body weight, age, sex and seriousness of diseases. For example, the range of dosages of the drugs in oral administration to adults can be approximately 0.01 to 0.45 mg/day of clonidine hydrochloride, 0.01 to 0.45 mg/day of moxonidine, 0.05 to 2.0 mg/day of rilmenidine, 0.01 to 0.45 mg/day of medetomidine, 0.01 to 0.45 mg/day of dexmedetomidine, 0.01 to 1.5 mg/day of guanfacine hydrochloride, 0.1 to 20.0 mg/day of guanabenz, 0.01 to 10.0 mg/day of α-methylnoradrenaline, 10.0 to 2,500 mg/day of methyldopa, 0.01 to 0.45 mg/day of UK14304, 0.01 to 0.45 mg/day of B-HT920 and 0.1 to 4.5 mg/day of B-HT933.

[0020] As β_2 AR stimulants, any known β_2 AR stimulant may be used. Such drugs include, for example, procaterol, ritodrine, terbutaline, salbutamol, clenbuterol, tulobuterol, mabuterol, salmeterol, formoterol, isoprenaline, trimetoquinol, hexoprenaline, methoxyphenamine, orciprenaline and fenoterol.

[0021] A dosage of a β_2 AR stimulant may be determined as needed according to individual β_2 AR stimulant, patients' body weight, age, sex and seriousness of diseases. For example, the range of dosages of the drugs in oral administration to adults can be approximately 0.001 to 0.2 mg/day of procaterol hydrochloride, 0.01 to 150 mg/day of ritodrine hydrochloride, 0.01 to 15 mg/day of terbutaline sulfate, 0.01 to 15 mg/day of salbutamol sulfate, 0.001 to 0.1 mg/day of clenbuterol hydrochloride, 0.1 to 10 mg/day of tulobuterol hydrochloride, 0.01 to 0.1 mg/day of mabuterol hydrochloride, 0.01 to 0.1 mg/day of salmeterol xinafoate, 0.01 to 0.2 mg/day of formoterol fumarate, 0.1 to 15 mg/day of isoprenaline hydrochloride, 0.1 to 20 mg./day of trimetoquinol hydrochloride, 0.001 to 0.02 mg/day of hexoprenaline, 10 to 300 mg/day of methoxyphenamine hydrochloride, 0.5 to 100 mg/day of orciprenaline sulfate and 0.1 to 10 mg/day of fenoterol hydrobromide. The dosages of β_2 AR stimulants used may be also reduced when used in combination with α_2 AR stimulants.

[0022] A combination formulation of the present invention that contains an α_2 AR stimulant and a β_2 AR stimulant includes a single formulation containing an α_2 AR stimulant and a β_2 AR stimulant, a single formulation containing a compound that has both α_2 AR stimulation and β_2 AR stimulation activities, a formulation in a package that contains the combination of a formulation containing an α_2 AR stimulant and a formulation containing a β_2 AR stimulant, and a combination of a formulation containing an α_2 AR stimulant and a formulation containing a β_2 AR stimulant that are co-administered simultaneously or at intervals in the same administration form or different administration forms.

[0023] As the compounds that have both α_2 AR stimulation and β_2 AR stimulation activities of the present invention, a compound which has the binding ability to α_2 AR no greater than 10^{-4} mol/L as the IC_{50} value and the binding ability to β_2 AR no greater than 10^{-5} mol/L as the IC_{50} value is preferable. An example of such a compound is (-)-bis(2-[(2S)-2-[{(2R)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl) ethyl} amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-N, N-dimethylacetamide} sulfate dihydrate (hereinafter referred to as Compound 1). The Compound 1 can be manufactured easily in accordance with methods described in literatures (for example, see Patent reference 1).

[0024] Combination formulations of the present invention markedly increase the nociceptive threshold in models such as STZ-induced diabetic rats, which is the representative model for evaluation of drug efficacy in neuropathic pain, and therefore, are useful for the prevention or treatment of neuropathic pain. Neuropathic pain includes, for example, painful diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, phantom limb pain, causalgia, cancerous pain and postoperative or traumatic chronic pain.

[0025] Of combination formulations of the present invention, a single formulation containing an α_2 AR stimulant and a β_2 AR stimulant can be manufactured by admixing or by diluting and dissolving an α_2 AR stimulant and a β_2 AR stimulant with formulation carriers including necessary excipients, disintegrators, binders, lubricants, diluents, buffers, isotonic agents, antiseptics, humectants, emulsifiers, dispersing agents, stabilizers and solubilizers or the like in various dosage forms in the usual way. When an α_2 AR stimulant and a β_2 AR stimulant are administered as separate formulations,

single formulations of each agent that are available may be used.

[0026] Examples of administration forms of the pharmaceutical composition of the present invention are forms administered orally such as powders, granules, fine granules, dry syrup, tablets, capsules or the like, forms administered non-orally such as injections, poultices, suppositories or the like. Forms administered orally is preferable.

[0027] A pharmaceutical composition of the present invention may be used occasionally in combination with other drugs that have effects alleviating symptoms of neuropathic pain. Examples of other drugs that have effects alleviating symptoms of neuropathic pain include psychotropic vitamins such as vitamin B_{12} and so on; non-steroidal anti-inflammatory drugs such as indomethacin, diclofenac and so on; aldose reductase inhibitors such as epalrestat and so on; lidocaine-like antiarrhythmic drugs such as mexiletine, lidocaine and so on; antidepressants such as imipramine, amitriptine, mianserin and so on; and anticonvulsants such as carbamazepine, phenytoin and so on.

Example

[0028] The present invention is further illustrated in more detail by way of the following Examples. However, the present invention is not limited thereto.

[Test Example 1] Measurement of the nociceptive threshold in STZ-induced diabetic rats (single administration)

[0029] STZ (50 mg/kg) was administered intravenously to male SD stain rats to induce diabetes mellitus. Test articles were administered 14 days later (10 rats in each group). Test articles used were clonidine as the a_2 AR stimulant, terbutaline as the β_2 AR stimulant and the above-mentioned Compound 1. Normal and Control groups received the medium (0.5% methylcellulose). Before and one hour after administration of test articles, the nociceptive threshold against pressure stimulation given to the right hind-paw of rats was measured by Randall-Selitto method, and compared with that in Control group.

[Test Example 2] Measurement of the nociceptive threshold in STZ-induced diabetic rats (repeated administration)

[0030] STZ (50 mg/kg) was administered intravenously to male SD stain rats to induce diabetes mellitus. Beginning on the following day of STZ administration, each test article was administered orally once a day, repeatedly, 14 times in total (9 to 10 rats in each group). Normal and Control groups received the medium (0.5% methylcellulose). Before the final administration (before administration of test articles) and after the final administration (one hour after the administration), the nociceptive threshold against pressure stimulation given to the right hind-paw of rats was measured by Randall-Selitto method, and compared with that in Control group.

[Test Example 3] Measurement of the nociceptive threshold in Seltzer model rats (single administration)

[0031] Ten, 9-week old male SD rats were anesthetized with pentobarbital (Nembutal injection®), and the right sciatic nerve was exposed. In Nerve ligation group (7 rats), half of the dorsal portion of the nerve was ligated using 5-0 nylon thread. In Normal group (3 rats), the sciatic nerve was only exposed. Three weeks after the model was created, the control group received the medium (0.5% methylcellulose) and Nerve ligation group was given orally test articles. Before the administration (before administration of test articles) and after administration (one hour after the administration of test articles), the nociceptive threshold against pressure stimulation given to the right hind-paw of rats was measured by Randall-Selitto method. Results before and after administration were compared.

[Test Example 4] Measurement of the nociceptive threshold in Seltzer model rats (repeated administration)

[0032] Thirty, 7-week old male SD rats were anesthetized with pentobarbital (Nembutal injection®), and the right sciatic nerve was exposed. In the nerve ligation group (20 rats), half of the dorsal portion of the nerve was ligated using 6-0 silk thread. In the normal group (10 rats), the sciatic nerve was only exposed. Beginning the following day of the model creation, test articles were administered orally once a day, repeatedly, 14 times in total. Normal and Control groups received the medium (0.5% methyl-cellulose) and Nerve ligation group was given orally test articles. One hour after the final administration, the nociceptive threshold against pressure stimulation given to the right hind-paw of rats was measured by Randall-Selitto method, and compared with Control group.

[Test Example 5] Receptor binding tests of α_2 AR and β_2 AR

[0033] Receptor binding tests were conducted in ^{3}H-p-aminoclonidine and ^{3}H-dihydroalprenolol (3 rats in each) using specimens of the membrane of rat cerebral cortex (α_2 AR) and the fascia of gravid uterus (β_2 AR) as the sources of

receptors. The binding ability of Compound 1 to α_2 AR and β_2 AR were obtained by calculating binding inhibition rates (IC_{50} values) of Compound 1 against the binding abilities of the above-mentioned tracers with both receptors. As a result, the binding affinity (IC_{50} value) of Compound 1 to α_2 AR and β_2 AR was, in concentration, 5.8×10^{-7} mol/L and 1.4×10^{-8} mol/L, respectively.

[Example 1] Analgesic effects of α_2 AR stimulant and β_2 AR stimulant (single administration) in STZ-induced diabetic rats

[0034] In accordance with the method of Test Example 1, studied were analgesic effects of clonidine (L group: 0.1 mg/kg; H group: 1.0 mg/kg, administered by subcutaneous injection) and terbutaline (L group: 1 mg/kg; H group: 10 mg/kg, oral administration). Table 1 shows the nociceptive threshold (mean±SE) before and after administration of each group. In the table, the symbol "##" indicates P<0.01: significant difference from Control group (in Aspin-Welch's t test), and the symbol "**" indicates P<0.01: significant difference from Control group (in Steel test).

[0035] As a result, the nociceptive thresholds before administration were significantly lower in Control and Test article groups than in Normal group. There was no difference between Control and Test article groups. The nociceptive threshold after administration increased in clonidine H group, demonstrating an apparent analgesic effect in this dose compared with Control group.

[0036] [Table 1]

Table 1. Nociceptive threshold in STZ-induced diabetic rats (single administration)

Administration group	Dose (mg/ kg)	Nociceptive threshold before administration (g)	Nociceptive threshold after administration (g)
Normal group	-	302.6±15.7##	286.4±21.5##
Control group	-	119.2±11.7	121.4±11.8
Clonidine L group	0.1	122.8±7.5	155.8±16.3
Clonidine H group	1.0	115.4±8.9	325.8±29.8**
Terbutaline L group	1.0	134.2±6.3	152.8±12.7
Terbutaline H group	10.0	122.6±14.5	146.8±20.7

[Example 2] Analgesic effects of α_2 AR stimulant and β_2 AR stimulant (repeated administration) in STZ-induced diabetic rats

[0037] In accordance with the method of Test Example 2, studied were analgesic effects of repeatedly administered clonidine (L group: 0.1 mg/kg; M group: 0.3 mg/kg; H. group: 1.0,mg/kg, administered by subcutaneous injection) and terbutaline (L group: 1 mg/kg; M group: 3 mg/kg; H group: 10 mg/kg; oral administration). Table 2 shows the nociceptive threshold (mean±SE) after administration in each group. In the table, the symbol "##" indicates P<0.01: significant difference from Control group (in Aspin-Welch's t test), and the symbol "*" indicates P<0.05 and "**" indicates P<0.01: significant differences from Control group (in Steel test).

[0038] As a result, following repeated administration of clonidine or terbutaline for 14 days, the nociceptive threshold increased significantly only in clonidine H group and terbutaline H group.

[0039] [Table 2]

Table 2. Nociceptive threshold in STZ-induced diabetic rats (repeated administration)

Administration group	Dose (mg/kg)	Nociceptive threshold before administration (g)	Nociceptive threshold after administration (g)
Normal group	-	297.6±25.2##	306.6±26.9##
Control group	-	109.6±8.7	119.8±13.7
Clonidine L group	0.1	129.2±15.9	180.6±24.4
Clonidine M group	0.3	104.2±13.8	115.2±18.2
Clonidine H group	1.0	97.2±14.5	254.4±33.3*
Terbutaline L group	1.0	113.8±11.9	115.2±12.6

(continued)

Administration group	Dose (mg/kg)	Nociceptive threshold before administration (g)	Nociceptive threshold after administration (g)
Terbutaline M group	3.0	155.4±32.0	167.8±32.3
Terbutaline H group	10.0	228.2±11.1**	229.0±14.8**

[Example 3] Analgesic effects of α_2 AR stimulant and β_2 AR stimulant used solely and in combination (repeated administration) in STZ-induced diabetic rats

[0040] In accordance with the method of Test Example 2, studied were analgesic effects of repeatedly administered clonidine (L group: 0.1 mg/kg; M group: 0.3 mg/kg, administered by subcutaneous injection), terbutaline (L group:1 mg/kg; M group: 3 mg/kg, oral administration), and combination (L-L group: co-administration of clonidine 0.1 mg/kg and terbutaline 1 mg/kg; L-M group: co-administration of clonidine 0.1 mg/kg and terbutaline 3 mg/kg, group; M-L group: co-administration of clonidine 0.3 mg/kg and terbutaline 1 mg/kg; and M-M group: co-administration of clonidine 0.3 mg/kg and terbutaline 3 mg/kg). Figure 1 shows the nociceptive threshold (mean±SE) after administration in each group.

[0041] As a result, after a 14-day repeated, sole administration of clonidine or terbutaline, in neither L groups or M groups of either test articles, the nociceptive threshold increased. While, in all combination groups comprising in combination each dose that solely had no action clearly increased nociceptive thresholds. The effects were synergistic, exceeding sum of effects in nociceptive threshold in sole administration of each agent. In all combination groups, nociceptive thresholds improved nearly to that in Normal group.

[Example 4] Analgesic effects of a compound that has both α_2 AR stimulation and β_2 AR stimulation activities (single administration) in.STZ-induced diabetic rats

[0042] In accordance with the method of Test Example 1, studied was anti-nociceptive action of Compound 1 (0.3, 1, 3 and 10 mg/kg, oral administration). Table 3 shows nociceptive thresholds (mean±SE) after administration in each group. In the table, the symbol "#" indicates $P<0.05$: significant difference from Control group (in Aspin-Welch's t test), and the symbol "*" indicates $P<0.05$: significant difference from Control group (in Steel test).

[0043] As a result, in each group receiving Compound 1, the nociceptive thresholds after administration increased dose-dependently. Groups receiving 3 mg/kg and 10 mg/kg of Compound 1 demonstrated apparent analgesic effects.

[0044] [Table 3]

Table 3. Nociceptive threshold in STZ-induced diabetic rats (single administration)

Administration group	Dose (mg/kg)	Nociceptive threshold before administration (g)	Nociceptive threshold after administration (g)
Normal group	-	298.2±35.7#	283.2±28.1#
Control group	-	86.8±7.7	91.8±8.7
Compound 1	0.3	71.8±5.3	117.6±10.7
Compound 1	1.0	95.0±5.1	131.0±12.3
Compound 1	3.0	92.0±13.3	174.6±15.4*
Compound 1	10.0	89.0±10.2	253.4±28.3*

[Example 5] Analgesic effects of a compound that has both α_2 AR stimulation and β_2 AR stimulation activities (repeated administration) in.STZ-induced diabetic rats

[0045] In accordance with the method of Test Example 2, studied were analgesic effects of repeatedly administered Compound 1 (0.3, 1, 3 and 10 mg/kg, oral administration). Figure 2 shows nociceptive thresholds (mean±SE) after Administration in each group.

[0046] As a result, after a 14-day repeated oral administration of Compound 1, the nociceptive thresholds after administration clearly increased dose-dependently beginning at dosage of 0.3 mg/kg. Repeated administration of Compound 1 demonstrated stronger effect increasing the nociceptive threshold than single administration, and improved the nociceptive threshold to the same level as in Normal group. The results confirmed that a compound that has both α_2

AR stimulation and β_2 AR stimulation activities also manifests apparent analgesic effect as the co-administration of both stimulants.

[Example 6] Analgesic effect of a compound that has both α_2 AR stimulation and β_2 AR stimulation activities (single administration) in Seltzer model

[0047] In accordance with the method of Test Example 3, studied was analgesic effect of Compound 1 (10 mg/kg, oral administration). Figure 3 shows the nociceptive thresholds (mean±SE) before and after administration in each group.
[0048] As a result, 3 weeks after model was created, the nociceptive threshold of the right hind-paw of Nerve ligation group decreased significantly compared with that of Normal group. Following administration of Compound 1, the nociceptive threshold of Nerve ligation group improved significantly in comparison with that before administration.

[Example 7] Analgesic effect of a compound that has both α_2 AR stimulation and β_2 AR stimulation activities (repeated administration) in Seltzer model

[0049] In accordance with the method of Test Example 4, studied was analgesic effect of repeatedly administered Compound 1 (10 mg/kg, oral administrat.ion). Figure 4 shows the nociceptive thresholds (means±SE) before and after administration in each group.
[0050] As a result, following a 14-day repeated administration of Compound 1, the nociceptive threshold of the right hind-paw improved significantly in comparison with that of Control group.
[0051] As described, a β_2 AR stimulant in sole administration showed analgesic action. Particularly, when a β_2 AR stimulant was combined with an α_2 AR stimulant, the combination demonstrated synergistic analgesic action at doses each of that had no analgesic action in sole administration of either agent. Similar to the co-administration of both stimulants, a compound that had both α_2 AR stimulation and β_2 AR stimulation activities exhibited apparent analgesic action. Thus, the uses of β2 AR stimulants, particularly in combination with α_2 AR stimulants, increased markedly the nociceptive thresholds in STZ-induced diabetic rats and Seltzer model rats, and therefore, are extremely useful for the prevention or treatment of neuropathic pain.

Industrial applicability

[0052] The pharmaceutical compositions of the present invention are extremely useful as agents.for the prevention or treatment of neuropathic pain.

Claims

1. A formulation for the prevention or treatment of neuropathic pain, which comprises a β_2-adrenoceptor stimulant as an active ingredient.

2. A formulation for the prevention or treatment of neuropathic pain as claimed in claim 1, which comprises the combination of an α_2-adrenoceptor stimulant and a β_2-adrenoceptor stimulant.

3. A formulation as claimed in claim 2, which comprises as an active ingredient a compound that has both α_2-adrenoceptor stimulation and β_2-adrenoceptor stimulation activities.

4. A formulation as claimed in any of claims 1 to 3, wherein neuropathic pain is painful diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, phantom limb pain, causalgia, cancerous pain, or postoperative or traumatic chronic pain.

5. A formulation as claimed in any of claims 1 to 4, which can be used in combination with one or more of drugs selected from a group consisting of a psychotropic vitamins, a non-steroidal anti-inflammatory drug, an aldose reductase inhibitor, a lidocaine-like anti-arrhythmic drug, an antidepressant and an anticonvulsant.

6. A method of the prevention or treatment of neuropathic pain, which comprises repeated administration of effective doses of a β_2-adrenoceptor stimulant for 2 weeks or longer.

7. A method of the prevention or treatment of neuropathic pain; which comprises administration of effective doses of the combination of an α_2-adrenoceptor stimulant and a β_2-adrenoceptor stimulant.

8. A use of a β_2-adrenoceptor stimulant for the manufacture of a formulation for the prevention or treatment of neuropathic pain.

9. A use of an α_2-adrenoceptor stimulant and a β_2-adrenoceptor stimulant for the manufacture of a formulation the prevention or treatment of neuropathic pain.

[Fig.1]

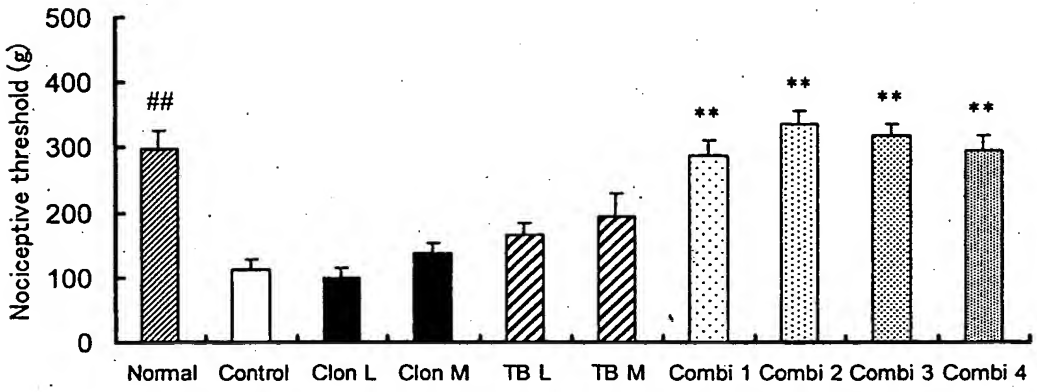


Fig.1 Effect on nociceptive threshold in STZ-induced diabetic rat by repeated administration of sole or combination of an α_2AR stimulant and a β_2AR stimulant

[Fig.2]

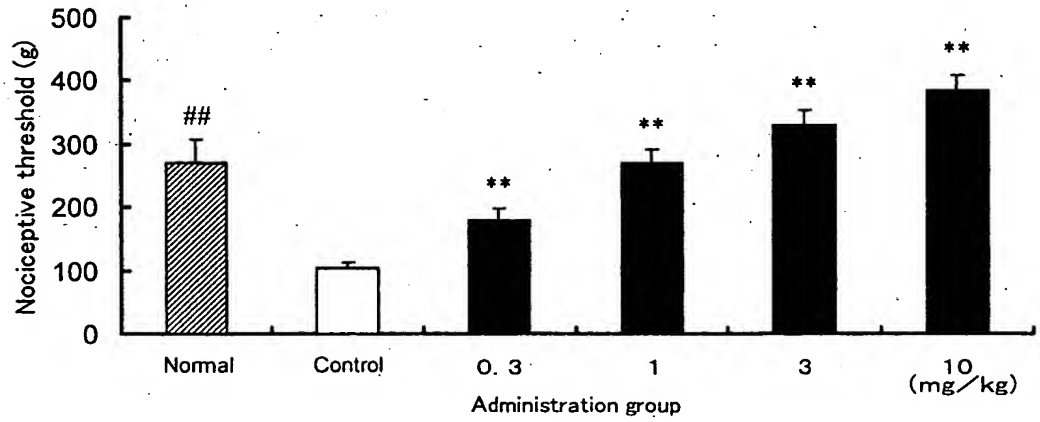
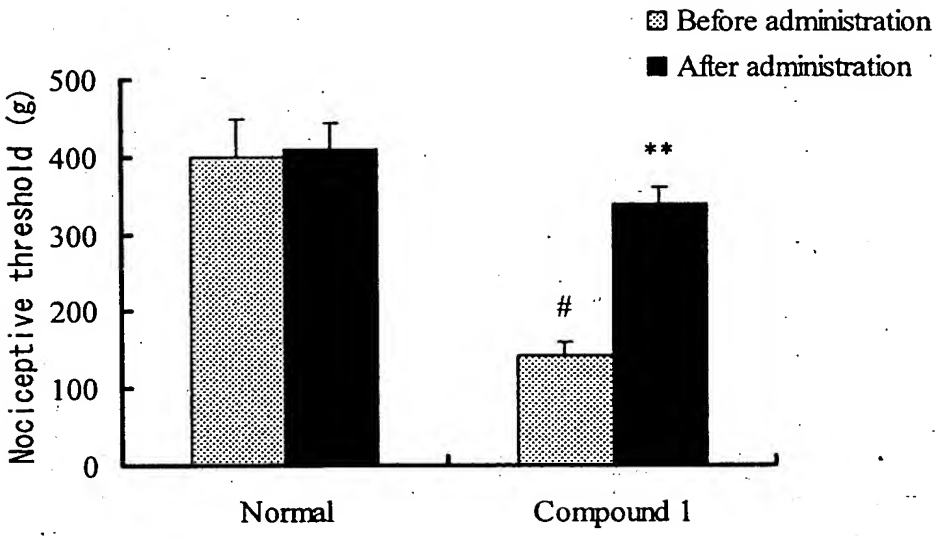
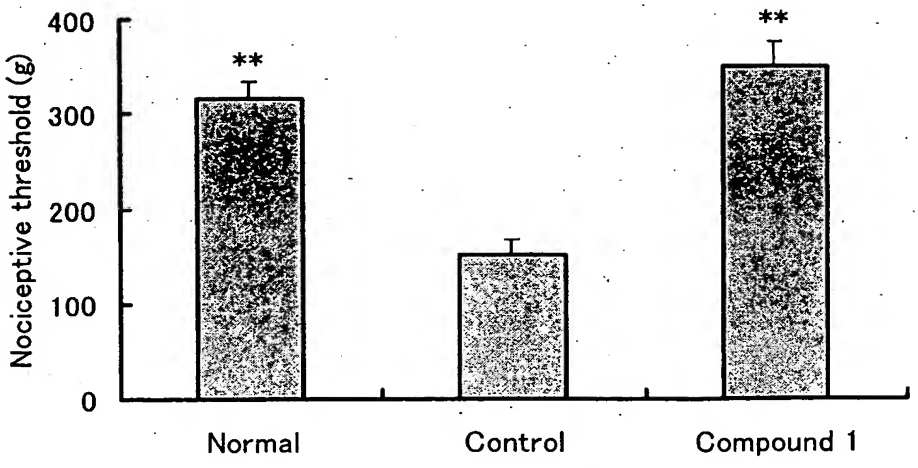


Fig.2 Effect on nociceptive threshold in STZ-induced diabetic rat by repeated administration of Compound 1

[Fig.3]


Before administration
After administration
Nociceptive threshold (g)
500
400
300
200
100
0
**
#
Normal
Compound 1

[Fig.4]


Nociceptive threshold (g)
400
300
200
100
0
**
**
Normal
Control
Compound 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/020830

A. CLASSIFICATION OF SUBJECT MATTER
A61K45/06(2006.01), ***A61K45/00***(2006.01), ***A61K31/137***(2006.01), ***A61K31/165***(2006.01), ***A61K31/4168***(2006.01), ***A61P29/00***(2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K45/06(2006.01), ***A61K45/00***(2006.01), ***A61K31/137***(2006.01), ***A61K31/165***(2006.01), ***A61K31/4168***(2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Jitsuyo Shinan Toroku Koho 1996-2006
Kokai Jitsuyo Shinan Koho 1971-2006 Toroku Jitsuyo Shinan Koho 1994-2006

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
REGISTRY(STN), CAPLUS(STN), MEDLINE(STN), BIOSIS(STN), EMBASE(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 2000-503628 A (L'Oreal), 28 March, 2000 (28.03.00), Full text; particularly, Claims; page 4, line 27 to page 5, line 27; page 6, lines 26 to 29; examples 1, 2 & EP 769293 A2 & WO 97/15281 A1 & FR 2740040 A & NO 9706143 A & US 5958432 A	1-5,8,9
Y	JP 2000-502690 A (Janssen Pharmaceutica N.V.), 07 March, 2000 (07.03.00), Full text; particularly, page 26, line 3 to page 28, line 5 & WO 97/24324 A1 & AU 9713084 A & EP 855999 A1 & NO 9802404 A & CN 1206406 A & KR 99076716 A & US 6169097 B1	1-5,8,9

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January, 2006 (12.01.06)	24 January, 2006 (24.01.06)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/020830

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 2002-020287 A (Pfizer Products Inc.), 23 January, 2002 (23.01.02), Full text; particularly, Claim 37 & CA 2345760 A1 & EP 1172106 A2 & AU 200142047 A & US 2002/035147 A1 & KR 2001109078 A	1-5,8,9
Y	JP 2001-522847 A (Merck Sharp & Dohme Ltd.), 20 November, 2001 (01.11.01), Full text; particularly, Par. Nos. [0033], [0034] & WO 99/24423 A1 & AU 9897554 A & EP 1028957 A1 & US 2002/052504 A1	1-5,8,9
Y	WO 2002/089794 A1 (UNIVERSITE CATHOLIQUE DE LOUVAIN), 14 November, 2002 (14.11.02), Full text; particularly, Claims & US 2003/022926 A1	2-5,9
Y	Shuji DOHI, "Nonopioid Chintsuyaku", Japanese Journal of Clinical Medicine, 2001, Vol.59, No.9, pages 1800 to 1805	2-5,9
Y	Shuji DOHI, "Sekizui ni Okeru α_2-Adrenaline Juyotai no Chintsu Kiko", Igaku no Ayumi, 1995, Vol.173, No.8, pages 691 to 695	2-5,9
Y	WO 97/30023 A1 (Kissei Pharmaceutical Co., Ltd.), 21 August, 1997 (21.08.97), Full text; particularly, example 7 & AU 9720014 A & NO 9803777 A & EP 882704 A1 & CN 1216526 A & US 6133266 A & KR 99082638 A	1-5,8,9

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/020830

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 6, 7
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 6 and 7 pertain to methods for treatment of the human body by surgery or therapy and diagnostic methods and thus relate to a subject matter which this International Searching Authority is not required to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

the

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, payment of a protest fee..

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/020830

<Subject of search>

Claims 1 to 5, 8 and 9 relate to a preventive or therapeutic preparation for neuropathic pains, comprising as an active ingredient any of compounds defined by desired properties, such as "β_2 adrenaline receptor stimulant", "α_2 adrenaline receptor stimulant" and "compound having both α_2 adrenaline receptor stimulating potency and β_2 adrenaline receptor stimulating potency". It appears that only some particular of the compounds with the above properties are supported by the description within the meaning of PCT Article 6 and disclosed therein within the meaning of PCT Article 5.

Further, with respect to any of the "β_2 adrenaline receptor stimulant", "α_2 adrenaline receptor stimulant" and "compound having both α_2 adrenaline receptor stimulating potency and β_2 adrenaline receptor stimulating potency", the scope of compounds with respective properties cannot be identified even if technical common knowledge at the time of filing of this application is taken into account.

Therefore, search has been restricted to the relationship between β_2 adrenaline receptor stimulating potency and/or α_2 adrenaline receptor stimulating potency and neuropathic pains, and to preventive or therapeutic preparations for neuropathic pains, comprising, as an active ingredient, terbutaline or compound (1) particularly set forth in the description.

Form PCT/ISA/210 (extra sheet) (April 2005)

REFERENCES CITED IN THE DESCRIPTION

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Non-patent literature cited in the description

- **KATSUYUKI MORIWAKI et al.** *Pain Clinic,* May 2000, vol. 21, S101-S107 **[0009]**
- **SHUJI DOHI.** *The Japanese Journal of Clinical Medicine,* 2001, vol. 59, 1800-1805 **[0009]**
- **FREDERIC DUFLO et al.** *Anesthesiology,* 2002, vol. 97, 636-641 **[0009]**
- New Pharmacology. Nankodo, 2002, 227-236 **[0009]**
- **MARY A. COTTER et al.** *European Journal of Pharmacology,* 1998, vol. 343, 217-223 **[0009]**